

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Roderick J. Scott	Art Unit	: 1638
Serial No.	: 10/058,825	Examiner	: Stuart F. Baum
Filed	: January 30, 2002	Conf. No.	: 2437
Title	: METHODS FOR MODIFYING PLANT ENDOSPERM		

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Commissioner for Patents

P.O. Box 1450

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BRIEF ON APPEAL

(1) Real Party in Interest

The real parties in interest are the University of Bath, Bath, United Kingdom, as assignee, and Ceres, Inc., Thousand Oaks, California, as licensee.

(2) Related Appeals and Interferences

There are no related appeals or interferences.

(3) Status of Claims

Claims 20-21, 62-67, 69, 71, 76-78 and 80-93 are pending and stand finally rejected.

Claims 1-19 and 23-39 were cancelled in a Response to Non-Compliant Amendment dated July 28, 2004.

Claim 22, 40-61, 68, 70, 75, and 79 were cancelled in a Response to Office Action dated February 25, 2005.

Claim 72-74 were cancelled in a Response to Final Office Action with a Request for Continued Examination dated November 7, 2005.

(4) Status of Amendments

All claim amendments were entered prior to the final Office Action, and no claim amendments are pending.

(5) Summary of Claimed Subject Matter

This invention relates to methods for the production of modified endosperm, involving the use of a partial or full-length DNA methyltransferase sequence to downregulate methyltransferase gene expression in female germ line cells. The prior art discloses the use of constitutive promoters linked to DNA methyltransferase sequences. The presently claimed invention involves the use of female germ line cell promoters linked to either partial or full-length *Arabidopsis* DNA methyltransferase 1 sequences, or partial or full-length *Zea mays* orthologs. Independent claim 20 specifies that the DNA methyltransferase sequence is a partial or full-length *Arabidopsis* DNA methyltransferase I (Met1) sequence. Independent claim 62 specifies that the DNA methyltransferase sequence is a partial or full-length sequence of the *Z. mays* ortholog to Met1. Such targeted expression is useful for producing modified endosperm, e.g., seeds with increased seed weight. The presently claimed invention is not taught or suggested by the prior art.

Claim 20 recites a method for producing modified endosperm. See, e.g., specification at page 12, lines 21-26; page 16, lines 9-11; and page 25, lines 16-20. The method comprises introducing a nucleic acid into a plant. E.g., specification at page 16, lines 10-11. The nucleic acid comprises a promoter targeting expression to female germ line cells and a partial or full-length *Arabidopsis* DNA methyltransferase I (Met1) sequence. See, e.g., specification at page 15, lines 1-10; page 16, lines 9-15; page 18, lines 26-30; and page 29, lines 10-28. The nucleic acid is effective for downregulating DNA methylating enzyme(s) and reducing the degree of DNA methylation. E.g., specification at page 18, lines 23-30; page 29, lines 10-28; page 30, lines 15-28; page 31, lines 12-28; and page 32, lines 1-8.

Claim 62 recites a method for producing modified endosperm. See, e.g., specification at page 12, lines 21-26; page 16, lines 9-11; and page 25, lines 16-20. The method comprises introducing a nucleic acid into a plant. E.g., specification at page 16, lines 10-11. The nucleic acid comprises a female germ line promoter and a partial or full-length *Z. mays* ortholog of the *Arabidopsis* Met1 sequence. See, e.g., specification at page 15, lines 1-10; page 16, lines 9-15; page 18, lines 26-30; page 29, lines 10-28; and page 32, lines 1-8. The nucleic acid is effective for downregulating DNA methylating enzyme(s) and reducing the degree of DNA methylation.

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See, e.g., specification at page 18, lines 23-30; page 29, lines 10-28; page 30, lines 15-28; page 31, lines 12-28; and page 32, lines 1-8.

(6) Grounds of Rejection to be Reviewed on Appeal

Rejection 1: Claims 20-21, 62-67, 69, 71, 76-78 and 80-93 stand rejected under 35 U.S.C. §112, second paragraph for indefiniteness.

Rejection 2: Claims 20-21, 62-67, 69, 71, 76-78 and 80-93 stand rejected under 35 U.S.C. §112, first paragraph for lack of written description.

Rejection 3: Claims 20-21, 62-67, 69, 71, 76-78 and 80-93 stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement.

(7) Argument

Rejection 1: Whether claims 20-21, 62-67, 69, 71, 76-78 and 80-93 satisfy the definiteness requirement.

A. Grouping of Claims for Rejection #1

Claims 20-21, 62-67, 69, 71, 76-78 and 80-93 stand or fall together.

B. Arguments for Reversal of Rejection #1

The Examiner rejected claim 20 and its dependent claims, asserting that the phrase “a sequence whose transcription product comprises a partial or full length Arabidopsis DNA methyltransferase (Met1) sequence” is indefinite. According to the Examiner, the Applicant stated in a prior Response that “the designation Arabidopsis Met1 will always refer to the sequence of Accession No. L10692 . . .” and that since Accession No. L10692 is a DNA sequence “it is unclear how a transcription product can be a DNA sequence and not a mRNA sequence.” Office Action of October 19, 2006 at pages 3-4.

The Examiner rejected claim 62 and its dependent claims, asserting that the phrase “a sequence whose transcription product comprises a partial or full length Zea mays sequence orthologous to the Arabidopsis methyltransferase (Met1) sequence” is indefinite for the same reason as for claim 20. Office Action of October 19, 2006 at page 4.

The Examiner maintained that given Applicant's explicit statement that “Met1 will *always* refer the sequence of Accession No. L10692,” the claims are unclear. Office Action of October 19, 2006 at page 4 (emphasis in original).

The test for definiteness under 35 U.S.C. § 112, second paragraph, is whether “those skilled in the art would understand what is claimed when the claim is read in light of the specification.” Orthokinetics, Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). A claim that appraises one of ordinary skill in the art of its scope serves the notice function required by 35 U.S.C. § 112, second paragraph. See, e.g., Solomon v. Kimberly-Clark Corp., 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000). That is, a claim that has a reasonable degree of clarity and precision for one of ordinary skill is sufficiently definite, whether or not the claim is as written the Examiner would desire.

Here, one of ordinary skill would understand what is claimed based on basic tenets of molecular biology, i.e., that the transcription product of an *Arabidopsis* Met1 sequence (or the *Z. mays* ortholog) is an RNA sequence that is a faithful copy of the DNA template from which the transcription product was transcribed. That is, one of ordinary skill would immediately understand that the DNA and RNA sequences of Accession No. L10692 are the same, with U (uracil) substituted for T (thymine).

References previously cited during prosecution to show that the designation *Arabidopsis* Met1 sequence refers to the sequence of Accession No. L10692 indicate that the DNA sequence of L10692 was itself derived from an RNA sequence. A copy of Genbank Accession No. L10692 is enclosed as Evidence Appendix A. For example, the previously cited Finnegan, et al., article states at page 2385, right-hand column that:

The length of the methyltransferase cDNA assembled from the overlapping cDNA clones Yc8 and Yc2 is 4720bp not including a poly A tail (Accession No. L10692), which agrees with the estimate based on Northern analysis of 4.7kb (data not shown).

Finnegan, et al., Nucleic Acids Res. 21: 2383-2388 (1993). Evidence Appendix B. Thus, the authors of Finnegan et al. created cDNAs from an *Arabidopsis* RNA, sequenced the cDNAs and deposited the resulting nucleotide sequence as Accession No. L10692. The results presented in the Finnegan et al. article show that the sequence presented in Accession No. L10692 was derived from an RNA sequence and that the DNA and RNA sequences are the same, with U substituted for T. One of ordinary skill would immediately understand that the transcription product of Accession No. L10692 is an RNA that has the same sequence as L10692, with U substituted for T.

In summary, the evidence above and the record as a whole demonstrate one of ordinary skill would understand that the transcription product of Accession No. L10692 is an RNA sequence. One of ordinary skill would understand that such a transcription product has the same sequence as Accession No. L10692 with U substituted for T, because the sequence of L10692 was itself derived from an RNA sequence. Thus, the claims are sufficiently definite to one of ordinary skill in the art. The Board is requested to reverse the Examiner's rejection of claims 20-21, 62-67, 69, 71, 76-78 and 80-93 under 35 U.S.C. §112, first paragraph, for indefiniteness.

Rejection 2: Whether Applicant's specification satisfies the written description requirement with respect to the subject matter of claims 20-21, 62-67, 69, 71, 76-78 and 80-93.

A. Grouping of Claims for Rejection #2

Each claim stands or falls separately from every other claim since the scope of these claims varies from claim to claim. For example, any finding of lack of written description for a genus claim does not necessarily mean a species claim within that genus lacks written description.

B. Arguments for Reversal of Rejection #2

The Examiner rejected claims 20-21, 62-67, 69, 71, 76-78 and 80-93 for lack of written description.

The Examiner acknowledged that the specification discloses a DNA sequence having accession number L10692 and that this sequence was known in the art. Office Action of January 27, 2006 at pages 5-6. The Examiner, however, interpreted "a partial" sequence to comprise any two consecutive amino acids from Arabidopsis or Zea mays DNA methyltransferase 1 (Met1) protein. Office Action of January 27, 2006 at page 7. Alternatively, the Examiner interpreted a partial sequence to comprise any dinucleotide of the Arabidopsis Met1 sequence. Office Action of October 19, 2006 at page 7.

The Examiner then alleged that "Applicants have not disclosed a representative number of sequences from a representative number of plants, encoding an Arabidopsis Met1 homologous protein." The Examiner further stated that the "Office contends Applicant has not disclosed a representative number of partial Met1 sequences, or even full length sequences that can be used to down regulate one or more DNA methylating enzymes and produce a plant whose seeds have a modified endosperm." Office Action of October 19, 2006 at pages 5-6. See also, Office Action of January 27, 2006 at pages 5-6. The Examiner further alleged that "Applicants have not disclosed essential elements of the genus of partial or full length Arabidopsis Met1 sequences," or "structural features common to members of the claimed genus of polynucleotides." Hence, according to the Examiner, "Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*." Office Action of January 27, 2006 at page 6.

The Examiner further alleged that "Applicants have not disclosed a single partial sequence that can be used to down-regulate one or more methylating enzymes present in a plant and produce plants whose seeds have a modified endosperm." Office Action of October 19, 2006 at page 5.

Written description is a question of fact, judged from the perspective of one of ordinary skill in the art. See Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). Compliance with § 112 requires sufficient information in the specification to show that the inventor possessed the invention as of the relevant filing date. See Vas-Cath, 935 F.2d at 1563-64 ("[T]he applicant must . . . convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention."); Union Oil Co. of Cal. v. Atl. Richfield Co., 208 F.3d 989, 997 (Fed. Cir. 2000) ("The written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.'" (citation omitted)). More recently, the Federal Circuit has held that "(1) examples are not necessary to support the adequacy of a written description (2) the written description standard may be met [] even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." Falkner v. Inglis, 448 F.3d 1357, 1366 (Fed. Cir. 2006). Falkner also states that "the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification." Falkner at 1368.

The discussion below is organized into two sections, one section discussing independent claim 20 and its dependent claims, and a second section discussing independent claim 62 and its dependent claims. Applicant believes that this organization will allow the Board to more conveniently follow Applicant's arguments concerning the limitations in each of the claims.

i) Claim 20 and Claims Dependent Therefrom

Claim 20

Claim 20 is directed to a method comprising introducing a nucleic acid comprising a female germ line promoter and a partial or full-length *Arabidopsis* DNA methyltransferase I

(Met1) sequence. The present specification provides more than adequate written description for the use of female germ line promoters and the Arabidopsis Met1 sequence to achieve targeted downregulation of DNA methylating enzymes and modification of endosperm.

First, the present specification clearly indicates the inventor considered part of the invention to be methods involving the use of an Arabidopsis Met1 sequence to downregulate DNA methylation. The instant specification states in the context of decreasing the degree of methylation that "the transgene can incorporate sequences which cause down regulation of methylating enzymes already present in the plant, and states that "[f]or example, one can use antisense sequences, e.g., the Met1 as 'gene'." Specification at page 18, lines 26-28.

Second, the present specification clearly indicates the inventor considered part of the invention to be the use of a female germ line promoter to downregulate DNA methyltransferases. For example, the instant specification indicates that "[e]xpression of the MET1 gene can be reduced in the female or male germ lines by employing techniques known in the art. For example MET1 down-regulation can be achieved by expressing antisense MET1 or antisense MET1 fragments or sense MET1 or partial sense MET1 or ribozymes directed against MET1 or combinations of the preceding, from promoters expressed in the required germ-line." Specification at page 30, lines 15-19.

Third, the present specification discloses a working example using a partial Met1 sequence. Example 3 describes the preparation of a construct having a partial Arabidopsis Met1 antisense sequence targeted to the female germ line. Example 4 describes its use to produce modified endosperm. Examples 3-4, pages 30-32.

Fourth, the Arabidopsis Met1 sequence was known in the art. See, e.g., Finnegan et al., Nucleic Acids Res. 23:2383-2388 (1993). Evidence Appendix B. The specification indicates that the Arabidopsis Met1 sequence is published as Accession No. L10692. The specification indicates that "down-regulation can be achieved by expressing antisense MET1 or antisense MET1 fragments or sense MET1 or partial sense MET1 or ribozymes directed against MET1 or combinations of the preceding, from promoters expressed in the required germ-line." Specification at page 30, lines 16-19. Rather than mechanically reciting partial Arabidopsis Met1 sequences in the specification, Applicant referred to partials of the known sequence because one of ordinary skill would have easily visualized the identity of partial Arabidopsis Met1 sequences

based on the full-length sequence. That is, a partial or full-length *Arabidopsis* Met1 sequence is not a new or unknown biological material that one of ordinary skill would easily miscomprehend. Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2003).

The Examiner has acknowledged that the *Arabidopsis* Met1 nucleotide sequence was known. However, the Examiner has chosen to interpret “a partial sequence” as comprising any two consecutive amino acids from the *Arabidopsis* Met1 protein, or alternatively, as any dinucleotide from the *Arabidopsis* Met1 DNA sequence. Based on this interpretation, the Examiner has resorted to the language of the Lilly case, stating that a representative number of *Arabidopsis* Met1 sequences are not disclosed in the specification and that structural features common to members of the genus are not disclosed. The Examiner has also insisted that the lack of an explicit definition of “partial” in the specification is fatal to the Applicant’s claims. Office Action of October 19, 2006 at page 7.

The Examiner’s interpretation of “partial” is contrary to the evidence. A Declaration under 37 CFR § 1.132 by Dr. Steven Jacobsen (hereinafter, the “Jacobsen Declaration”) was submitted with the Response of July 27, 2006. Evidence Appendix C. Dr. Jacobsen is a Professor at the University of California, Los Angeles, an Investigator in the Howard Hughes Medical Institute and a Fellow of the American Association for the Advancement of Science. Jacobsen Declaration at paragraphs 2-5. Dr. Jacobsen has conducted research in the genetics of DNA methylation patterning in *Arabidopsis* and genome wide analysis of DNA methylation since 1997. Jacobsen Declaration at paragraphs 2-5. Thus, Dr. Jacobsen is eminently qualified to discuss the genetics and biochemistry of DNA methylation in plants.

As stated in the Jacobsen Declaration, one of ordinary skill in the art would not have interpreted a partial *Arabidopsis* Met1 sequence as used in the claim to comprise only two consecutive nucleotides. One of ordinary skill would have known that sequences having only 2 nucleotides of sequence identity are too short to stably hybridize to a complementary sequence such that downregulation can occur. Jacobsen Declaration at paragraphs 10-11.

Here, rather than fully consider the Jacobsen Declaration, the Examiner merely responded by stating that the claim lacks written description because there is no explicit definition of a partial sequence in the specification. Office Action of October 19, 2006 at page 7. The

Examiner is expected to analyze and consider affidavits or declarations submitted in response to a written description rejection. In re Alton, 76 F.3d 1168, 1176, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996). The Examiner's apparent failure to consider the Jacobsen Declaration is contrary to Alton.

The Examiner's interpretation of "partial" is also contrary to the standards for claim interpretation during prosecution. The Examiner is to give claims their broadest reasonable interpretation consistent with the specification, as they would be understood by one of ordinary skill in the art. Phillips v. AWH Corp., 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005); In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997); In re Cortright, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999). Here, the Examiner has required that the word "partial" be defined in the specification rather than interpreting it as it would have been understood by one of ordinary skill in the art. Jacobsen Declaration at paragraphs 10-11. This is contrary to established law.

The Examiner's reliance on Lilly is misplaced. Lilly is inapposite when "the claim terms at issue [] are not new or unknown biologicals that ordinarily skilled artisans would easily miscomprehend." Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2003). Here, a partial or full-length Arabidopsis Met1 sequence is not a new or unknown biological material that one of ordinary skill would easily miscomprehend because the Arabidopsis Met1 sequence was already known.

The Examiner further alleged that "Applicants have not disclosed a single partial sequence that can be used to down-regulate one or more methylating enzymes present in a plant and produce plants whose seeds have a modified endosperm." Office Action of October 19, 2006 at page 5. In particular, the Examiner alleged that Example 3 is a prophetic example and that the specification does not disclose any partial sequences that can be used to down-regulate one or more DNA methylating enzymes and produce a plant whose seeds have a modified endosperm. Office Action of October 19, 2006 at page 7.

An Examiner should not normally question the results of tests and examples unless there is a reasonable basis for doing so. MPEP § 707.07(I). Here, the Examiner has concluded that Examples 3 and 4 are false, rather than present a reasonable basis for doubting the truth of Examples 3 and 4.

Example 3 describes the construction of a female germ line specific vector, pAGL5-asMET1, containing a partial *Arabidopsis* Met1 antisense sequence. See, page 30, line 21 to page 31, line 2. Example 3 indicates that such a construct downregulates Met1 expression. See, page 30, lines 15-19. Example 4 describes the transformation of *Arabidopsis* with pAGL5-asMET1 and states that such plants were vegetatively normal and produced flowers with the normal complement of floral organs. Specification at page 31, lines 16-17. Example 4 goes on to present data obtained from such plants following pollination with wild-type pollen. Endosperm development in the resulting seeds was monitored by confocal microscopy. Seed weights were measured at maturity. Data for the average maximum endosperm size, relative delay in cellularisation, chalazal endosperm hyperplasia, and mean seed weight are presented. See, page 31, lines 18-28 and Table 1. In the absence of any reasonable basis to question the information and data in Examples 3 and 4, such information and data must be accepted as true.

Applicant referred to the Federal Circuit decisions in Capon and Falkner concerning the written description requirement. Capon v. Eshar v. Dudas, 418 F.3d 1349 (Fed. Cir. 2005), Falkner v. Inglis, 448 F.3d 1357, 79 U.S.P.Q.2d 1001 (Fed. Cir. 2006) The Examiner dismissed these cases, stating that “the fact pattern of the instant application is not the same as the fact pattern associated with the Capon and Falkner cases. In the Capon case the claims were drawn to chimeric proteins, wherein the pieces which made up the chimeric proteins were known in the art. In the Falkner case, the claimed sequences were known in the art. In the instant application, the Office contends the genus of Met1 sequences is not known in the art.” Office Action of October 19, 2006 at page 5.

Applicant recognizes that the fact pattern of the present application is not the same as the fact pattern of the Capon and Falkner decisions. However, the issue is not whether the fact patterns are the same, the issue is whether Federal Circuit precedent is being followed. The Federal Circuit held in Falkner that “(1) examples are not necessary to support the adequacy of a written description (2) the written description standard may be met [] even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.” Falkner v. Inglis, 448 F.3d 1357, 79 U.S.P.Q.2d 1001 (Fed. Cir. 2006). Merely because the fact patterns are not the same is insufficient basis to dismiss Capon

and Falkner. The claim is directed specifically to the *Arabidopsis* Met1 sequence and fragments thereof. The complete *Arabidopsis* Met1 sequence was known from Accession No. L10692. One of ordinary skill would have easily comprehended the identity of partial *Arabidopsis* Met1 sequences based on the full-length sequence. One of ordinary skill would not have interpreted a partial *Arabidopsis* Met1 sequence as used in the claim to comprise only two consecutive nucleotides. The *per se* requirement for a mechanical recitation of partial and full-length *Arabidopsis* Met1 sequences in order to satisfy the written description requirement is inconsistent with Falkner.

In summary, the *Arabidopsis* Met1 sequence was known in the art. The present specification describes the use of partial and full-length *Arabidopsis* Met1 sequences in conjunction with female germ line promoters to downregulate DNA methylating enzymes. There is a working example in the specification of the construction and use of a partial Met1 sequence and female germ line promoter for downregulation. The Jacobsen Declaration shows that the Examiner's interpretation of a partial *Arabidopsis* Met1 sequence is unreasonable. The Examiner has not fully considered the Jacobsen Declaration, and has not followed the standards for claim interpretation during prosecution. The Board is requested to withdraw the rejection of claim 20 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 21

Claim 21 limits the transcription product of claim 20 to an antisense nucleic acid. Applicant traverses the rejection of claim 21 for the reasons given above and the following reasons. The instant specification states in the context of decreasing the degree of methylation that "one can use antisense sequences, e.g., the Met1as 'gene'." Specification at page 18, lines 26-28. The instant specification indicates that "MET1 down-regulation can be achieved by expressing antisense MET1 or antisense MET1 fragments [], from promoters expressed in the required germ-line." Specification at page 30, lines 15-19. The present specification discloses a working Example using an *Arabidopsis* partial Met1 sequence in the specification at Examples 3-4, pages 30-32. The Board is requested to withdraw the rejection of claim 21 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 64

Claim 64 limits the plant of claim 20 to a dicotyledonous plant. Applicant traverses the rejection of claim 64 for the reasons given above and the following reasons. The working Example in the specification used a dicotyledonous plant, *Arabidopsis thaliana*. The specification states that the invention is to be used with dicotyledonous plants. See, for example, specification at page 1, line 33 to page 2, line 5, and at page 32, lines 6-9. The Board is requested to withdraw the rejection of claim 64 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 65

Claim 65 limits the transcription product of claim 20 to one that downregulates one DNA methylating enzyme. Applicant traverses the rejection of claim 65 for the reasons given above and the following reasons. The specification states at page 18, lines 26-27, that "the transgene can incorporate sequences which cause down regulation of methylating enzymes already present in the plant." Original claim 20 recites downregulation of one or more methylating enzymes. The Board is requested to withdraw the rejection of claim 65 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 66

Claim 66 limits the transcription product of claim 20 to a full or partial sense copy of the Arabidopsis Met1 sequence. Applicant traverses the rejection of claim 66 for the reasons given above with respect to claim 20. The Board is requested to withdraw the rejection of claim 66 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 67

Claim 67 limits claim 66 by requiring that the transcription product be a partial sense copy. Applicant traverses the rejection of claim 67 for the reasons given above with respect to claim 20. The Board is requested to withdraw the rejection of claim 67 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 71

Claim 71 limits the plant of claim 66 to a dicotyledonous plant. Applicant traverses the rejection of claim 71 for the reasons given above with respect to claims 64 and 66. The Board is requested to withdraw the rejection of claim 71 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 77

Claim 77 limits the promoter of claim 20 to one that targets expression in female gametic cells. Applicant traverses the rejection of claim 77 for the reasons given above and the following reasons. The specification clearly indicates that the regulatory sequence is "capable of directing expression in the male or female germ line and/or gametes of the resultant plant . . ." The Board is requested to withdraw the rejection of claim 77 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 78

Claim 78 limits the transcription product of claim 77 to an antisense nucleic acid. Applicant traverses the rejection of claim 78 for the reasons given above, including the reasons given for claims 77 and 21. The Board is requested to withdraw the rejection of claim 78 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 80

Claim 80 limits the transcription product of claim 77 to a full or partial sense copy of the Arabidopsis Met1 sequence. Applicant traverses the rejection of claim 80 for the reasons given above, including the reasons given for claims 77 and 66. The Board is requested to withdraw the rejection of claim 80 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 81

Claim 81 limits the plant of claim 77 to a dicotyledonous plant. Applicant traverses the rejection of claim 81 for the reasons given above, including the reasons given for claims 77 and 64. The Board is requested to withdraw the rejection of claim 81 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 82

Claim 82 limits the plant of claim 77 to a monocotyledonous plant. Applicant traverses the rejection of claim 82 for the reasons given above and the following reasons. The specification discusses techniques for transforming monocots at page 21, lines 12-14. The specification indicates at page 32, lines 6-9, that the female germ line/Met1 antisense vector, pAGL5Met1as, could be transformed into *Zea mays*, which is a monocot. One of ordinary skill would have been aware that Met1 nucleotide sequences have a high degree of sequence identity and that there are regions that are highly conserved. See, e.g., Finnegan et al., Ann. Rev. Plant

Physiol. Plant Mol. Biol. 49:223-247 (1998) at pages 227-229. Evidence Appendix D. An example is found in the attached diagram at Appendix E, which shows an alignment of DNA methyltransferase sequences from *Arabidopsis* and *Zea mays*. The overall nucleotide sequence identity between the *Arabidopsis* and *Zea* sequences is about 64%. Moreover, there are numerous regions in these sequences that have greater than 75% identity. See, e.g., nucleotides 731 to 856 (76% identity), nucleotides 3329 to 3981 (82% identity), 3635 to 3720 (91% identity), and nucleotides 4331 to 4590 (82% identity). These are strikingly high percent identities given that *Arabidopsis* is a dicot and *Zea* is a monocot. In view of the above, there is more than adequate written description for the use of monocot plants. The Board is requested to withdraw the rejection of claim 82 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 83

Claim 83 limits the dicotyledonous plant of claim 81 to a *Brassica* plant. Applicant traverses the rejection of claim 83 for the reasons given above and the following reasons. Examples 3 and 4 of the specification describe the use of *Arabidopsis thaliana*, which is a member of the *Brassicaceae* family. *Brassica* spp. are also members of the *Brassicaceae* family. The specification indicates at page 32, lines 6-9, that the female germ line/Met1 antisense vector, pAGL5Met1as, could be transformed into *Brassica napus*, which is a species in the *Brassica* genus. The Board is requested to withdraw the rejection of claim 83 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 84

Claim 84 limits the dicotyledonous plant of claim 81 to a *Brassica napus* plant. Applicant traverses the rejection of claim 84 for the reasons given above, including the reasons given for claims 81 and 83. The Board is requested to withdraw the rejection of claim 84 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 85

Claim 85 limits the monocotyledonous plant of claim 82 to a *Zea mays* plant. Applicant traverses the rejection of claim 85 for the reasons given above with respect to claims 77 and 82. The Board is requested to withdraw the rejection of claim 85 for lack of written description under 35 U.S.C. §112, first paragraph.

ii) Claim 62 and Claims Dependent Therefrom

Claim 62 recites that the method comprises introducing a nucleic acid into a plant. The nucleic acid comprises a female germ line promoter and a partial or full-length *Z. mays* ortholog of the *Arabidopsis* Met1 sequence. The nucleic acid is effective for downregulating DNA methylating enzyme(s) and reducing the degree of DNA methylation. The present specification provides more than adequate written description for such a method.

First, the present specification clearly indicates the inventor considered part of the invention to be methods involving the use of a *Z. mays* Met1 ortholog sequence to downregulate DNA methylation. The instant specification states in the context of decreasing the degree of methylation that “the transgene can incorporate sequences which cause down regulation of methylating enzymes already present in the plant, and states that “[f]or example, one can use antisense sequences, e.g., the Met1 as ‘gene’.” Specification at page 18, lines 26-28.

Second, the present specification clearly indicates the inventor considered part of the invention to be the use of a female germ line promoter to downregulate DNA methyltransferases. For example, the instant specification indicates that “[e]xpression of the MET1 gene can be reduced in the female or male germ lines by employing techniques known in the art. For example MET1 down-regulation can be achieved by expressing antisense MET1 or antisense MET1 fragments or sense MET1 or partial sense MET1 or ribozymes directed against MET1 or combinations of the preceding, from promoters expressed in the required germ-line.” Specification at page 30, lines 15-19.

Third, the *Z. mays* Met1 ortholog sequence was known in the art. See, e.g., Genbank Accession Number AF063403. Evidence Appendix F. The complete carrot, *Arabidopsis*, pea and tomato Met1 sequences were known from the earliest priority date from Genbank Accession Numbers AF007807, L10692, AF034419 and AJ002140. Evidence Appendices G, A, H, I. There are numerous regions in these sequences that are highly conserved even though *Zea mays* is a monocot and the remainder are dicots, directing one of ordinary skill to partial sequences that would have been effective for downregulation in heterologous species. Rather than mechanically reciting partial *Z. mays* Met1 sequences in the specification, Applicant referred to partials of the known sequence because one of ordinary skill would have easily visualized the identity of partial *Z. mays* ortholog sequences based on the full-length sequence. That is, a partial

or full-length *Z. mays* ortholog sequence is not a new or unknown biological material that one of ordinary skill would easily miscomprehend. Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2003).

The Examiner has acknowledged that the *Z. mays* ortholog nucleotide sequence was known. However, the Examiner has chosen to interpret “a partial sequence” as comprising any two consecutive amino acids from the *Z. mays* ortholog Met1 protein, or alternatively, as any dinucleotide from the *Z. mays* ortholog Met1 DNA sequence. Based on this interpretation, the Examiner has resorted to the language of the Lilly case, stating that a representative number of *Z. mays* ortholog sequences are not disclosed in the specification and that structural features common to members of the genus are not disclosed. The Examiner has also insisted that the lack of an explicit definition of “partial” in the specification is fatal to the Applicant’s claims. Office Action of October 19, 2006 at page 7.

The Examiner’s interpretation of “partial” is contrary to the evidence. A Declaration under 37 CFR § 1.132 by Dr. Steven Jacobsen (hereinafter, the “Jacobsen Declaration”) was submitted with the Response of July 27, 2006. Evidence Appendix C. Dr. Jacobsen is a Professor at the University of California, Los Angeles, an Investigator in the Howard Hughes Medical Institute and a Fellow of the American Association for the Advancement of Science. Jacobsen Declaration at paragraphs 2-5. Dr. Jacobsen has conducted research in the genetics of DNA methylation patterning in *Arabidopsis* and genome wide analysis of DNA methylation since 1997. Jacobsen Declaration at paragraphs 2-5. Thus, Dr. Jacobsen is eminently qualified to discuss the genetics and biochemistry of DNA methylation in plants.

As stated in the Jacobsen Declaration, one of ordinary skill in the art would not have interpreted a partial *Z. mays* Met1 sequence as used in the claims to comprise only two consecutive nucleotides. One of ordinary skill would have known that sequences having only 2 nucleotides of sequence identity are too short to stably hybridize to a complementary sequence such that downregulation can occur. Jacobsen Declaration at paragraphs 10-11.

Here, rather than consider the Jacobsen Declaration, the Examiner merely responded by stating that the claim lacks written description because there is no explicit definition of a partial sequence in the specification. Office Action of October 19, 2006 at page 7. The Examiner is expected to analyze and consider affidavits or declarations submitted in response to a written

description rejection. In re Alton, 76 F.3d 1168, 1176, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996). The Examiner's apparent failure to consider the Jacobsen Declaration is contrary to Alton.

The Examiner's interpretation of "partial" is also contrary to the standards for claim interpretation during prosecution. The Examiner is to give claims their broadest reasonable interpretation consistent with the specification, as they would be understood by one of ordinary skill in the art. Phillips v. AWH Corp., 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005); In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997); In re Cortright, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999). Here, the Examiner has required that the word "partial" be defined in the specification rather than interpreting it as it would have been understood by one of ordinary skill in the art. Jacobsen Declaration at paragraphs 10-11. This is contrary to established law.

The Examiner's reliance on Lilly is misplaced. Lilly is inapposite when "the claim terms at issue [] are not new or unknown biologicals that ordinarily skilled artisans would easily miscomprehend." Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2003). Here, a partial or full-length Z. mays ortholog Met1 sequence is not a new or unknown biological material that one of ordinary skill would easily miscomprehend because the Z. mays ortholog Met1 sequence was already known.

The Examiner further alleged that "Applicants have not disclosed a single partial sequence that can be used to down-regulate one or more methylating enzymes present in a plant and produce plants whose seeds have a modified endosperm." Office Action of October 19, 2006 at page 5. In particular, the Examiner alleged that Example 3 is a prophetic example and that the specification does not disclose any partial sequences that can be used to down-regulate one or more DNA methylating enzymes and produce a plant whose seeds have a modified endosperm. Office Action of October 19, 2006 at page 7.

An Examiner should not normally question the results of tests and examples unless there is a reasonable basis for doing so. MPEP § 707.07(I). Here, the Examiner has concluded that Examples 3 and 4 are false, rather than present a reasonable basis for doubting the truth of Examples 3 and 4.

Example 3 describes the construction of a female germ line specific vector, pAGL5-asMET1, containing a partial *Arabidopsis* Met1 antisense sequence. See, page 30, line 21 to

page 31, line 2. Example 3 indicates that such a construct downregulates Met1 expression. See, page 30, lines 15-19. Example 4 describes the transformation of *Arabidopsis* with pAGL5-asMET1 and states that such plants were vegetatively normal and produced flowers with the normal complement of floral organs. Specification at page 31, lines 16-17. Example 4 goes on to present data obtained from such plants following pollination with wild-type pollen. Endosperm development in the resulting seeds was monitored by confocal microscopy. Seed weights were measured at maturity. Data for the average maximum endosperm size, relative delay in cellularisation, chalazal endosperm hyperplasia, and mean seed weight are presented. See, page 31, lines 18-28 and Table 1. In the absence of any reasonable basis to question the information and data in Examples 3 and 4, the Examiner must accept such information and data as true.

Applicant referred to the Federal Circuit decisions in Capon and Falkner concerning the written description requirement. Capon v. Eshar v. Dudas, 418 F.3d 1349 (Fed. Cir. 2005), Falkner v. Inglis, 448 F.3d 1357, 79 U.S.P.Q.2d 1001 (Fed. Cir. 2006) The Examiner dismissed these cases, stating that “the fact pattern of the instant application is not the same as the fact pattern associated with the Capon and Falkner cases. In the Capon case the claims were drawn to chimeric proteins, wherein the pieces which made up the chimeric proteins were known in the art. In the Falkner case, the claimed sequences were known in the art. In the instant application, the Office contends the genus of Met1 sequences is not known in the art.” Office Action of October 19, 2006 at page 5.

Applicant recognizes that the fact pattern of the present application is not the same as the fact pattern of the Capon and Falkner decisions. However, the issue is not whether the fact patterns are the same, the issue is whether Federal Circuit precedent is being followed. The Federal Circuit held in Falkner that “(1) examples are not necessary to support the adequacy of a written description (2) the written description standard may be met [] even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.” Falkner v. Inglis, 448 F.3d 1357, 79 U.S.P.Q.2d 1001 (Fed. Cir. 2006). Merely because the fact patterns are not the same is insufficient basis to dismiss Capon and Falkner. The claim is directed specifically to the *Z. mays* Met1 orthologous sequence and

fragments thereof. The complete *Z. mays* sequence was known from Accession No. AF063403. One of ordinary skill would have easily comprehended the identity of partial *Z. mays* orthologous sequences based on the full-length sequence. One of ordinary skill would not have interpreted a partial *Z. mays* sequence as used in the claim to comprise only two consecutive nucleotides. The *per se* requirement for a mechanical recitation of partial and full-length *Z. mays* sequences in order to satisfy the written description requirement is inconsistent with Falkner.

In summary, the *Z. mays* ortholog sequence was known in the art. The present specification describes the use of partial and full-length *Z. mays* ortholog sequences in conjunction with female germ line promoters to downregulate DNA methylating enzymes. There is a working example in the specification of the construction and use of an Arabidopsis partial Met1 sequence and female germ line promoter for downregulation. The Jacobsen Declaration shows that the Examiner's interpretation of a partial *Z. mays* ortholog sequence is unreasonable. The Examiner has not presented any reasoning or evidence to rebut the Jacobsen Declaration, has not followed the standards for claim interpretation during prosecution, and has not followed Federal Circuit precedent. The Board is requested to withdraw the rejection of claim 62 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 63

Claim 63 limits the method of claim 62 to one in which the transcription product comprises an antisense nucleic acid. Applicant traverses the rejection for the reasons given above with respect to claims 21 and 62. The Board is requested to withdraw the rejection of claim 62 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 69

Claim 69 limits the method of claim 62 to a transcription product that comprises a full or partial sense copy of the *Z. mays* sequence. Applicant traverses the rejection of claim 69 for the reasons given above with respect to claims 62 and 66. The Board is requested to withdraw the rejection of claim 69 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 76

Claim 76 limits claim 62 to a method in which the plant is a dicotyledonous plant. Applicant traverses the rejection of claim 76 for the reasons given above, in particular, with

respect to claims 62 and 64. The Board is requested to withdraw the rejection of claim 76 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 86

Claim 86 limits the method claim 62 to one in which the promoter targets expression to female gametic cells. Applicant traverses the rejection of claim 76 for the reasons given above, in particular, with respect to claims 62 and 77. The Board is requested to withdraw the rejection of claim 86 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 87

Claim 87 limits claim 86 to a method in which the transcription product comprises an antisense nucleic acid. Applicant traverses the rejection of claim 87 for the reasons given above, in particular, with respect to claims 62, 86 and 21. The Board is requested to withdraw the rejection of claim 87 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 88

Claim 88 limits the method of claim 86 to one in which the transcription product comprises a partial sense copy of the *Z. mays* sequence orthologous to *Arabidopsis* DNA methyltransferase 1 (Met1) sequence. Applicant traverses the rejection of claim 88 for the reasons given above, in particular, with respect to claims 62, 86 and 67. The Board is requested to withdraw the rejection of claim 88 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 89

Claim 89 limits the method of claim 86 to one in which the plant is a dicotyledonous plant. Applicant traverses the rejection of claim 89 for the reasons given above, in particular, with respect to claims 62, 76 and 86. The Board is requested to withdraw the rejection of claim 89 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 90

Claim 90 limits the method of claim 86 to one in which the plant is a monocotyledonous plant. Applicant traverses the rejection of claim 90 for the reasons given above including the reasons given for claims 86, 62 and 82. The Board is requested to withdraw the rejection of claim 90 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 91

Claim 91 limits the method of claim 89 to one in which the plant is a *Brassica* plant. Applicant traverses the rejection of claim 91 for the reasons given above, including the reasons given for claims 89, 86, 62 and 83. The Board is requested to withdraw the rejection of claim 91 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 92

Claim 92 limits the method of claim 89 to one in which the plant is a *B. napus* plant. Applicant traverses the rejection of claim 92 for the reasons given above, including the reasons given with respect to claims 89, 86, 62 and 83. The Board is requested to withdraw the rejection of claim 92 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 93

Claim 93 limits the method of claim 90 to one in which the plant is a *Zea mays* plant. Applicant traverses the rejection of claim 93 for the reasons given above, including the reasons given with respect to claims 90, 86, 62 and 82. The Board is requested to withdraw the rejection of claim 93 for lack of written description under 35 U.S.C. §112, first paragraph.

In summary, the evidence above and the record as a whole strongly support a conclusion that the present specification provides more than adequate written description for the pending claims to one of ordinary skill in the art. The Board is requested to reverse the Examiner's rejection of the pending claims under 35 U.S.C. §112, first paragraph, for lack of written description.

Rejection 3: Whether Applicant's specification satisfies the enablement requirement with respect to the subject matter of claims 20-21, 62-67, 69, 71, 76-78 and 80-93.

A. Grouping of Claims for Rejection #3

Each of claims 20-21, 62-67, 69, 71, 76-78 and 80-93, stand or fall separately since the scope of each claim varies. For example, a finding of lack of enablement for a genus claim does not necessarily mean a subgenus claim within that genus lacks enablement.

B. Arguments for Reversal of Examiner's Rejection #3

The Examiner rejected claims 20-21, 62-67, 69, 71, 76-78 and 80-93 for lack of enablement.

1) The Examiner interpreted "a partial" sequence to comprise any two consecutive amino acids from the Arabidopsis DNA methyltransferase 1 (Met1) protein. Office Action of January 27, 2006 at page 7. Alternatively, the Examiner interpreted a partial sequence to comprise any dinucleotide of the Arabidopsis Met1 sequence. Office Action of October 19, 2006 at page 9. The Examiner then asserted that given the lack of an explicit definition of "partial" the present claims are drawn to any dinucleotide of the Arabidopsis Met1 sequence. Office Action of October 19, 2006 at page 9.

2) The Examiner also alleged that the claims "do not specify that the promoter and sequence of interest be operably linked." Office Action of October 19, 2006 at page 9.

3) In view of the Examiner's interpretation of "partial," the Examiner maintained that there is a lack of guidance regarding which partial sequences of the Arabidopsis Met1 will downregulate DNA methylating enzymes. Office Action of October 19, 2006 at page 10.

4) The Examiner alleged that the art area is unpredictable, citing a number of references in the Office Action of January 27, 2006 as evidence for this proposition. The Examiner asserted that "Applicant has not disclosed any partial sequence of the Arabidopsis Met1 gene [] that can be used to down-regulate the full length endogenous gene in any plant, monocot or dicot, and produce seeds with a modified endosperm. Applicant has not shown that down-regulating any methyltransferase produces seeds with a modified endosperm" Office Action of October 19, 2006 at pages 11-12. The Examiner also alleged that "Applicant has not disclosed which regions of the Met1 gene can be used for down-regulating the endogenous gene that will not down-regulate the other multitude of methyltransferases present in a plant." Office Action of October 19, 2006 at page 12.

Enablement requires that the specification teach those in the art how to make and use the invention without "undue experimentation." *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is undertaken, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

Claims are to be given their broadest reasonable interpretation during prosecution. In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997). However, the interpretation must be consistent with the interpretation that would be given to the claims by one of ordinary skill in the art. In re Cortright, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999).

The discussion below is organized into two sections, one section discussing independent claim 20 and its dependent claims, and a second section discussing independent claim 62 and its dependent claims. Applicant believes that this organization will allow the Board to more conveniently follow Applicant's arguments concerning the limitations in each of the claims.

i) Claim 20 and Claims Dependent Therefrom

Claim 20

Claim 20 is directed to a method comprising introducing a nucleic acid comprising a female germ line promoter and a partial or full-length *Arabidopsis* DNA methyltransferase I (Met1) sequence. The present specification enables one of ordinary skill in the art to make and use female germ line promoters and the *Arabidopsis* Met1 sequence to achieve targeted downregulation of DNA methylating enzymes and modification of endosperm.

1) The Examiner has chosen to interpret "a partial sequence" as comprising any two consecutive amino acids from the *Arabidopsis* Met1 protein, or alternatively, as any dinucleotide from the *Arabidopsis* Met1 DNA sequence. The Examiner's interpretation of the word "partial" in the claims is contrary to the understanding of one of ordinary skill in the art. A Declaration under 37 CFR § 1.132 by Dr. Steven Jacobsen (the "Jacobsen Declaration") was submitted with the Response of July 27, 2006. Evidence Appendix C. Dr. Jacobsen is a Professor at the University of California, Los Angeles, an Investigator in the Howard Hughes Medical Institute and a Fellow of the American Association for the Advancement of Science. Jacobsen Declaration at paragraphs 2-5. Dr. Jacobsen has conducted research in the genetics of DNA methylation patterning in *Arabidopsis* and genome wide analysis of DNA methylation since 1997. Jacobsen Declaration at paragraphs 2-5. Thus, Dr. Jacobsen is eminently qualified to discuss the genetics and biochemistry of DNA methylation in plants.

As stated in the Jacobsen Declaration, one of ordinary skill in the art would not have interpreted a partial *Arabidopsis* Met1 sequence as used in the claims to comprise only two consecutive nucleotides. One of ordinary skill would have known that sequences having only 2 nucleotides of sequence identity are too short to stably hybridize to a complementary sequence such that downregulation can occur. Jacobsen Declaration at paragraphs 10-11. Thus, the Examiner's interpretation of "partial" is contrary to the understanding of one of ordinary skill.

In response to the Jacobsen Declaration, the Examiner merely stated that the claim is not enabled because there is no explicit definition of the word "partial" in the specification. Office Action of October 19, 2006 at page 9. Applicants submit that the Examiner has not given full and fair consideration to the substance of the Jacobsen Declaration. The Declaration by Dr. Jacobsen supports a conclusion that claim 20 is enabled, and the Examiner has provided no evidence that contradicts the Jacobsen Declaration.

The Examiner's interpretation of "partial" is also contrary to the standards for claim interpretation during prosecution. The Examiner is to give claims their broadest reasonable interpretation consistent with the specification, as they would be understood by one of ordinary skill in the art. Phillips v. AWH Corp., 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005); In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997); In re Cortright, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999). Here, the Examiner's interpretation is inconsistent with the specification as it would have understood by one of ordinary skill, in view of the Jacobsen Declaration.

2) The Examiner's interpretation that the claim does not specify that the promoter and the *Arabidopsis* Met1 sequence are operably linked is contrary to the interpretation that would have been given by one of ordinary skill. In re Morris and In re Cortright, supra. The Examiner's interpretation is also inconsistent with the plain language of the claim.

As indicated in the Jacobsen Declaration, one of ordinary skill would have interpreted the claim to mean that a promoter that targets expression to female germ line cells drives transcription of the indicated Met1 sequence. Jacobsen Declaration at paragraph 15. Furthermore, the plain language of the claim requires that the introduced nucleic acid is effective for down-regulating one or more DNA methylating enzymes present in the plant. A partial or

full-length *Arabidopsis* Met1 sequence that is not operably linked to the female germ line promoter would not be effective for downregulation.

Rather than address the merits of the Jacobsen Declaration or fully consider the plain language of the claim, the Examiner merely stated that limitations from the specification are not read into the claims. Office Action of October 19, 2006 at page 9. However, the Examiner has not indicated what limitation from the specification is being read into the claims. The reason the Examiner has not done so is because there is no such limitation. Instead, as stated in the Jacobsen Declaration, one of ordinary skill would have interpreted these claims to mean that a promoter that targets expression to female germ line cells drives transcription of the indicated *Arabidopsis* Met1 sequence.

In view of the evidence provided in the Jacobsen Declaration and the lack of any countervailing evidence provided by the Examiner, the Examiner's interpretation of the claim must be rejected.

3) Based on the Examiner's interpretation of "partial," the Examiner has maintained that there is a lack of guidance regarding which partial sequences of the *Arabidopsis* Met1 will downregulate DNA methylating enzymes and that there is no disclosure of which regions of the *Arabidopsis* Met1 sequence can be used for downregulation. Office Action of October 19, 2006 at page 10. The Examiner apparently has acknowledged that the principles of downregulation technologies would have been well known to one of ordinary skill at the time of filing, but stated that although there are reports of 3' and 5' regions that work to downregulate a gene, "not all 3' or 5' regions will work." Office Action of October 19, 2006 at page 9.

The Examiner's requirement for detailed recitations of partial *Arabidopsis* Met1 sequences that have been empirically tested misplaces the focus of the enablement inquiry on the length of the disclosure rather than its substance. As the Federal Circuit has held, "[n]ot every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be." See DeGeorge v. Bernier, 768 F.2d 1318 (Fed. Cir. 1985) and cases cited therein. The specification need not "necessarily describe how to make and use every possible variant of the claimed invention, for the artisan's knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps

even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art.” AK Steel Corp. v Sollac 344 F.3d 1234, 1244 (Fed. Cir. 2003). Indeed, “[n]othing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples.” In re Wright, 999 F.2d 1557 (Fed. Cir. 1993).

Here, the Examiner’s assertion that “not all 3’ or 5’ regions will work” is not enough to outweigh the evidence supporting enablement of the claim. The complete *Arabidopsis* Met1 sequence was known from Accession No. L10692. Evidence Appendix A. The claim is specifically directed to the *Arabidopsis* Met1 sequence and fragments thereof, and one of ordinary skill is thus immediately directed to the sequences to be used in the claimed method. The general principles of downregulation technologies were known. The complete carrot, corn, pea and tomato Met1 sequences were known from the earliest priority date from Genbank Accession Numbers AF007807, AF063403, AF034419 and AJ002140. Evidence Appendices G, F, H, and I. There are numerous regions in these sequences that are highly conserved even though *Zea mays* is a monocot and the remainder are dicots, directing one of ordinary skill to partial *Arobidopsis* Met1 sequences that would have been effective for downregulation in heterologous species. Methodologies for screening plants having partial *Arabidopsis* Met1 sequences for a decrease in the degree of overall DNA methylation were known. See, Jacobsen Declaration at paragraph 16. In fact, Dr. Jacobsen states that one of ordinary skill would have expected that in general heterologous partial sequences can be used to downregulate endogenous genes. Jacobsen Declaration at paragraph 23. In view of the specific recitation of the *Arabidopsis* Met1 sequence in the claim, the guidance provided in the specification to one of ordinary skill and the evidence presented in the Jacobsen Declaration, no more than routine experimentation would have been required to practice the full scope of the claim.

4) The Examiner cited a number of references in the Office Action of January 27, 2006 as evidence for the proposition that the art area is unpredictable. These references include the Fourgoux-Nicol, Emery, Gutterson and Jacobsen references. Evidence Appendices J, K, L, and M. In response to Applicant’s arguments submitted July 27, 2006, the Examiner dismissed Fourgoux-Nicol as no longer applicable. Office Action of October 19, 2006 at page 10. The

Examiner maintained that the previously cited Gutterson and Emery articles support a conclusion of unpredictability. Office Action of October 19, 2006 at page 10. The Examiner did not address Applicant's arguments regarding the Jacobsen reference.

According to the Examiner, the Fourgoux-Nicol et al. article is no longer applicable because the reason it was initially cited by the Examiner is no longer germane to prosecution. Office Action of October 19, 2006 at page 10. However, the Examiner has ignored the aspects of Fourgoux-Nicol that are germane to prosecution. In particular, paragraphs 17-20 of the Jacobsen Declaration point out that the data in the Fourgoux-Nicol article indicate the Arabidopsis Met1 sequence would hybridize to (and thereby downregulate) a heterologous sequence. The Examiner has not presented any evidence to rebut this conclusion.

The Examiner acknowledged that there are references disclosing the use of antisense or sense suppression technology, but then goes on to state that the "enablement rejection is directed toward the full breadth of the claims." Office Action of October 19, 2006 at page 11. The Examiner then reiterates his statement that the Applicant has not disclosed any partial sequence of the Arabidopsis Met1 gene that can be used to downregulate an endogenous gene in any plant. Office Action of October 19, 2006 at page 11. Thus, the Examiner's position appears to be that since there is a failure to disclose "partial" sequences, claim 20 is not enabled despite Applicant's arguments and the Declaration from Dr. Jacobsen.

The Examiner's argument is wrong on the facts and weak on logic. First, the specification does disclose that partial sequences are useful to downregulate methyltransferases and discloses a working example in which a partial Arabidopsis Met1 sequence was used to produce modified endosperm. See, for example, specification at page 30, lines 15-19 and pages 30-32, Examples 3-4.

Second, the Examiner's argument rests on the belief that the supposed "failure" to disclose partial Arabidopsis Met1 sequences outweighs the evidence in the Jacobsen Declaration and in Applicant's Response of July 27, 2006. Applicant's evidence can be summarized as follows. Dr. Jacobsen referred to publications that show the use of heterologous sequences to successfully downregulate an endogenous gene. Dr. Jacobsen concluded that sequences having less than 100% sequence identity to an endogenous gene can be used for downregulation. Jacobsen Declaration at paragraphs 21-27. The Emery reference cited by the Examiner is a post-

filing date reference that has no evidence of what one skilled in the art would have known on or before the effective filing date. Therefore, the Emery reference is not relevant to whether the claimed invention would have been enabled as of the effective filing date. In fact, the Emery reference actually demonstrates the precision with which one of ordinary skill can upregulate or downregulate a particular gene. The Jacobsen reference cited by the Examiner reported that there was a significant reduction in overall DNA methylation in the plant lines described in the Jacobsen reference. Jacobsen Declaration at paragraphs 12-14. Dr. Jacobsen was the first author of the Jacobsen reference cited by the Examiner. The Examiner did not respond to Applicant's arguments regarding the Jacobsen reference. Applicant submitted eight additional references that report downregulation using heterologous sequences, including sequences having less than 100% sequence identity to an endogenous gene. Evidence Appendix N. These other prior art references show one of ordinary skill would have concluded that antisense sequences with less than 100% sequence identity can be used to downregulate a heterologous endogenous gene.

Thus, the references cited by the Examiner and the Applicant support enablement. These references demonstrate a high level of skill in the art for downregulation technologies, and that those of ordinary skill knew how to make and use sequences for downregulation. The references demonstrate that the use of these technologies was predictable and required, at most, routine experimentation. These references and the Jacobsen Declaration outweigh the arguments the Examiner put forth.

The Examiner has now asserted that the Applicant has not shown that downregulating any methyltransferase produces seeds with modified endosperm. Office Action of October 19, 2006 at pages 11-12. The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Here, the Examiner did not present a reasonable basis to question enablement. Instead, the Examiner once again misstated the facts by alleging that the specification does not disclose a partial Arabidopsis Met1 sequence that produces seeds with a modified endosperm. In actuality, the specification at page 16, lines 8-28, page 18, lines 26-28 and pages 30-32, for example, disclose the construction of partial Arabidopsis Met1 sequences linked to a female germ line promoter, discloses their usefulness for downregulation and discloses the use of a construct to produce seeds with modified endosperm. The Examiner

asserted that "Applicant has not disclosed which regions of the Met1 gene can be used for down-regulating the endogenous gene that will not down-regulate the other multitude of methyltransferases present in a plant." Office Action of October 19, 2006 at pages 11-12. The Examiner's assertion acknowledges one point of Dr. Jacobsen's Declaration, namely, that partial and full-length Arabidopsis Met1 sequences could be expected to downregulate more than one endogenous DNA methyltransferase in non-Arabidopsis plants. Jacobsen Declaration at paragraphs 22-23. The present inventor recognized that if one targeted expression of partial or full-length Arabidopsis Met1 sequences to the female germ line, one would not need to use specific Arabidopsis Met1 sequences to downregulate specific DNA methyltransferases. In other words, it does not matter for enablement whether more than one DNA methyltransferase is downregulated, and the Examiner has given no reason why it does matter to his enablement rejection.

The Examiner has failed to identify a single reported instance where downregulation of a Met1 gene failed to reduce the degree of methylation. Applicants submit that the reason the Examiner has failed in his effort is because downregulation using the Arabidopsis Met1 sequence and constitutive promoters generally has been successful. As indicated in the Jacobsen Declaration and above, Applicant's claimed method involving the use of targeted promoters would also be expected to be generally successful, and the specification enables the pending claim for one of ordinary skill under a proper enablement standard.

In view of the facts and reasoning above and the record as a whole, the Board is requested to reverse the rejection of claim 20 under 35 U.S.C. §112, first paragraph for lack of enablement.

Claim 21

Claim 21 limits the transcription product of claim 20 to an antisense nucleic acid. Applicant traverses the rejection of claim 21 for the reasons given above and the following reasons. The instant specification states in the context of decreasing the degree of methylation that "one can use antisense sequences, e.g., the Met1as 'gene'." Specification at page 18, lines 26-28. The instant specification indicates that "MET1 down-regulation can be achieved by expressing antisense MET1 or antisense MET1 fragments [], from promoters expressed in the required germ-line." Specification at page 30, lines 15-19. The present specification discloses a

working Example using a partial Met1 antisense sequence in the specification at Examples 3-4, pages 30-32. The Board is requested to withdraw the rejection of claim 21 for lack of enablement under 35 U.S.C. §112, first paragraph.

Claim 64

Claim 64 limits the plant of claim 20 to a dicotyledonous plant. Applicant traverses the rejection of claim 64 for the reasons given above and the following reasons. The working Example in the specification used a dicotyledonous plant, *Arabidopsis thaliana*. The specification states that the invention is to be used with dicotyledonous plants. See, for example, specification at page 1, line 33 to page 2, line 5, and at page 32, lines 6-9. The Board is requested to withdraw the rejection of claim 64 for lack of enablement under 35 U.S.C. §112, first paragraph.

Claim 65

Claim 65 limits the transcription product of claim 20 to one that downregulates one DNA methylating enzyme. Applicant traverses the rejection of claim 65 for the reasons given above and the following reasons. The specification states at page 18, lines 26-27, that "the transgene can incorporate sequences which cause down regulation of methylating enzymes already present in the plant." Original claim 20 recites downregulation of one or more methylating enzymes. The Board is requested to withdraw the rejection of claim 65 for lack of enablement under 35 U.S.C. §112, first paragraph.

Claim 66

Claim 66 limits the transcription product of claim 20 to a full or partial sense copy of the *Arabidopsis* Met1 sequence. Applicant traverses the rejection of claim 66 for the reasons given above with respect to claim 20. The Board is requested to withdraw the rejection of claim 66 for lack of enablement under 35 U.S.C. §112, first paragraph.

Claim 67

Claim 67 limits claim 66 by requiring that the transcription product be a partial sense copy. Applicant traverses the rejection of claim 67 for the reasons given above with respect to claim 20. The Board is requested to withdraw the rejection of claim 67 for lack of enablement under 35 U.S.C. §112, first paragraph.

Claim 71

Claim 71 limits the plant of claim 66 to a dicotyledonous plant. Applicant traverses the rejection of claim 71 for the reasons given above with respect to claims 64 and 66. The Board is requested to withdraw the rejection of claim 71 for lack of enablement under 35 U.S.C. §112, first paragraph.

Claim 77

Claim 77 limits the promoter of claim 20 to one that targets expression in female gametic cells. Applicant traverses the rejection of claim 77 for the reasons given above and the following reasons. The specification clearly indicates that the regulatory sequence is "capable of directing expression in the male or female germ line and/or gametes of the resultant plant" The Examiner has provided no rationale for why undue experimentation would have been required for one of ordinary skill to make and use a method involving promoters targeting female gametic cells. The Board is requested to withdraw the rejection of claim 77 for lack of enablement under 35 U.S.C. §112, first paragraph.

Claim 78

Claim 78 limits the transcription product of claim 77 to an antisense nucleic acid. Applicant traverses the rejection of claim 78 for the reasons given above, including the reasons given for claims 77 and 21. The Board is requested to withdraw the rejection of claim 78 for lack of enablement under 35 U.S.C. §112, first paragraph.

Claim 80

Claim 80 limits the transcription product of claim 77 to a full or partial sense copy of the Arabidopsis Met1 sequence. Applicant traverses the rejection of claim 80 for the reasons given above, including the reasons given for claims 77 and 66. The Board is requested to withdraw the rejection of claim 80 for lack of enablement under 35 U.S.C. §112, first paragraph.

Claim 81

Claim 81 limits the plant of claim 77 to a dicotyledonous plant. Applicant traverses the rejection of claim 81 for the reasons given above, including the reasons given for claims 77 and 64. The Board is requested to withdraw the rejection of claim 81 for lack of enablement under 35 U.S.C. §112, first paragraph.

Claim 82

Claim 82 limits the plant of claim 77 to a monocotyledonous plant. Applicant traverses the rejection of claim 82 for the reasons given above and the following reasons. The specification discusses techniques for transforming monocots at page 21, lines 12-14. The specification indicates at page 32, lines 6-9, that the female germ line/Met1 antisense vector, pAGL5Met1as, could be transformed into *Zea mays*, which is a monocot. One of ordinary skill would have been aware that Met1 nucleotide sequences have a high degree of sequence identity and that there are regions that are highly conserved. See, e.g., Finnegan et al., *Ann. Rev. Plant Physiol. Plant Mol. Biol.* 49:223-247 (1998) at pages 227-229. Evidence Appendix D. An example is found in the attached diagram at Appendix E, which shows an alignment of DNA methyltransferase sequences from *Arabidopsis* and *Zea mays*. The overall nucleotide sequence identity between the *Arabidopsis* and *Zea* sequences is about 64%. Moreover, there are numerous regions in these sequences that have greater than 75% identity. See, e.g., nucleotides 731 to 856 (76% identity), nucleotides 3329 to 3981 (82% identity), 3635 to 3720 (91% identity), and nucleotides 4331 to 4590 (82% identity). These are strikingly high percent identities given that *Arabidopsis* is a dicot and *Zea* is a monocot and support the evidence in the Jacobsen Declaration at paragraphs 22-23. In view of the above, no more than routine experimentation would have been required for one of ordinary skill to make and use a partial or full-length *Arabidopsis* Met1 sequence in monocot plants. The Board is requested to withdraw the rejection of claim 82 for lack of enablement under 35 U.S.C. §112, first paragraph.

Claim 83

Claim 83 limits the dicotyledonous plant of claim 81 to a Brassica plant. Applicant traverses the rejection of claim 83 for the reasons given above and the following reasons. Examples 3 and 4 of the specification describe the use of *Arabidopsis thaliana*, which is a member of the Brassicaceae family. *Brassica* spp. are also members of the Brassicaceae family. The specification indicates at page 32, lines 6-9, that the female germ line/Met1 antisense vector, pAGL5Met1as, could be transformed into *Brassica napus*, which is a species in the *Brassica* genus. The Board is requested to withdraw the rejection of claim 83 for lack of enablement under 35 U.S.C. §112, first paragraph.

Claim 84

Claim 84 limits the dicotyledonous plant of claim 81 to a *Brassica napus* plant. Applicant traverses the rejection of claim 84 for the reasons given above including the reasons given for claims 81 and 83. The Board is requested to withdraw the rejection of claim 84 for lack of enablement under 35 U.S.C. § 112, first paragraph.

Claim 85

Claim 85 limits the monocotyledonous plant of claim 82 to a *Zea mays* plant. Applicant traverses the rejection of claim 85 for the reasons given above with respect to claims 77 and 82. The Board is requested to withdraw the rejection of claim 85 for lack of enablement under 35 U.S.C. § 112, first paragraph.

ii) Claim 62 and Claims Dependent Therefrom

Claim 62 is directed to a method comprising introducing a nucleic acid comprising a female germ line promoter and a partial or full-length *Z. mays* ortholog of the *Arabidopsis* Met1 sequence. The present specification enables one of ordinary skill in the art to make and use female germ line promoters and *Z. mays* orthologous sequences to achieve targeted downregulation of DNA methylating enzymes and modification of endosperm.

1) The Examiner has chosen to interpret “a partial sequence” as comprising any two consecutive amino acids from the *Z. mays* ortholog protein, or alternatively, as any dinucleotide from the *Z. mays* ortholog DNA sequence. The Examiner's interpretation of the word “partial” in the claims is contrary to the understanding of one of ordinary skill in the art. A Declaration under 37 CFR § 1.132 by Dr. Steven Jacobsen (the “Jacobsen Declaration”) was submitted with the Response of July 27, 2006. Evidence Appendix C. Dr. Jacobsen is a Professor at the University of California, Los Angeles, an Investigator in the Howard Hughes Medical Institute and a Fellow of the American Association for the Advancement of Science. Jacobsen Declaration at paragraphs 2-5. Dr. Jacobsen has conducted research in the genetics of DNA methylation patterning in *Arabidopsis* and genome wide analysis of DNA methylation since 1997. Jacobsen Declaration at paragraphs 2-5. Thus, Dr. Jacobsen is eminently qualified to discuss the genetics and biochemistry of DNA methylation in plants.

As stated in the Jacobsen Declaration, one of ordinary skill in the art would not have interpreted a partial Z. mays ortholog sequence as used in the claims to comprise only two consecutive nucleotides. One of ordinary skill would have known that sequences having only 2 nucleotides of sequence identity are too short to stably hybridize to a complementary sequence such that downregulation can occur. Jacobsen Declaration at paragraphs 10-11. Thus, the Examiner's interpretation of "partial" is contrary to the understanding of one of ordinary skill.

In response to the Jacobsen Declaration, the Examiner merely stated that the claim is not enabled because there is no explicit definition of the word "partial" in the specification. Office Action of October 19, 2006 at page 9. Applicants submit that the Examiner has not given full and fair consideration to the substance of the Jacobsen Declaration. The Declaration by Dr. Jacobsen supports a conclusion that the claim is enabled, and the Examiner has provided no evidence that contradicts the Jacobsen Declaration.

The Examiner's interpretation of "partial" is also contrary to the standards for claim interpretation during prosecution. The Examiner is to give claims their broadest reasonable interpretation consistent with the specification, as they would be understood by one of ordinary skill in the art. Phillips v. AWH Corp., 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005); In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997); In re Cortright, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999). Here, the Examiner's interpretation is inconsistent with the specification as it would have been understood by one of ordinary skill, in view of the Jacobsen Declaration.

2) The Examiner's interpretation that the claim does not specify that the promoter and the Z. mays ortholog sequence are operably linked is contrary to the interpretation that would have been given by one of ordinary skill. In re Morris and In re Cortright, supra. The Examiner's interpretation is also inconsistent with the plain language of the claim.

As indicated in the Jacobsen Declaration, one of ordinary skill would have interpreted the claim to mean that a promoter that targets expression to female germ line cells drives transcription of the indicated Met1 sequence. Jacobsen Declaration at paragraph 15. Furthermore, the plain language of the claim requires that the introduced nucleic acid is effective for down-regulating one or more DNA methylating enzymes present in the plant. A partial or

full-length *Z. mays* ortholog sequence that is not operably linked to the female germ line promoter would not be effective for downregulation.

Rather than address the merits of the Jacobsen Declaration or fully consider the plain language of the claim, the Examiner merely stated that limitations from the specification are not read into the claims. Office Action of October 19, 2006 at page 9. However, the Examiner has not indicated what limitation from the specification is being read into the claims. The reason the Examiner has not done so is because there is no such limitation. Instead, as stated in the Jacobsen Declaration, one of ordinary skill would have interpreted these claims to mean that a promoter that targets expression to female germ line cells drives transcription of the indicated *Z. mays* sequence.

In view of the evidence provided in the Jacobsen Declaration and the lack of any countervailing evidence provided by the Examiner, the Examiner's interpretation of the claim must be rejected.

3) Based on the Examiner's interpretation of "partial," the Examiner has maintained that there is a lack of guidance regarding which partial sequences of the *Z. mays* ortholog will downregulate DNA methylating enzymes and that there is no disclosure of which regions of the *Z. mays* ortholog sequence can be used for downregulation. Office Action of October 19, 2006 at page 10. The Examiner apparently has acknowledged that the principles of downregulation technologies would have been well known to one of ordinary skill at the time of filing, but stated that although there are reports of 3' and 5' regions that work to downregulate a gene, "not all 3' or 5' regions will work." Office Action of October 19, 2006 at page 9.

The Examiner's requirement for detailed recitations of partial *Zea mays* orthologous sequences that have been empirically tested misplaces the focus of the enablement inquiry on the length of the disclosure rather than its substance. As the Federal Circuit has held, "[n]ot every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be." See DeGeorge v. Bernier, 768 F.2d 1318 (Fed. Cir. 1985) and cases cited therein. The specification need not "necessarily describe how to make and use every possible variant of the claimed invention, for the artisan's knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps

even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art.” AK Steel Corp. v Sollac 344 F.3d 1234, 1244 (Fed. Cir. 2003). Indeed, “[n]othing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples.” In re Wright, 999 F.2d 1557 (Fed. Cir. 1993).

Here, the Examiner’s unsupported belief that “not all 3’ or 5’ regions will work” is not enough to outweigh the evidence supporting enablement of the claim. The complete *Zea mays* Met1 ortholog sequence was known from Genbank Accession No. AF063403. Evidence Appendix F. The claim is specifically directed to the *Zea mays* orthologous sequence and fragments thereof, and one of ordinary skill is thus immediately directed to the sequences to be used in the claimed method. The general principles of downregulation technologies were known. The complete Arabidopsis, carrot, pea and tomato Met1 sequences were known of the earliest priority date from Genbank Accession Numbers L10692, AF007807, AF034419 and AJ002140. Evidence Appendices A, G, H, I. There are numerous regions in these sequences that are highly conserved even though *Zea mays* is a monocot and the remainder are dicots, directing one of ordinary skill to partial *Zea mays* ortholog sequences that would have been effective for downregulation in heterologous species. Methodologies for screening plants having partial *Zea mays* orthologous sequences for a decrease in the degree of overall DNA methylation were known. See, Jacobsen Declaration at paragraph 16. In fact, Dr. Jacobsen states that one of ordinary skill would have expected that in general heterologous partial sequences can be used to downregulate endogenous genes. Jacobsen Declaration at paragraph 23. In view of the specific recitation of the *Zea mays* sequence in the claim, the guidance provided in the specification to one of ordinary skill and the evidence presented in the Jacobsen Declaration, no more than routine experimentation would have been required to practice the full scope of the claim.

4) The Examiner cited a number of references in the Office Action of January 27, 2006 as evidence for the proposition that the art area is unpredictable. These references include the Fourgoux-Nicol, Emery, Gutterson and Jacobsen references. Evidence Appendices J, K, L, M. In response to Applicant’s arguments submitted July 27, 2006, the Examiner dismissed Fourgoux-Nicol as no longer applicable. Office Action of October 19, 2006 at page 10. The

Examiner maintained that the previously cited Gutterson and Emery articles support a conclusion of unpredictability. Office Action of October 19, 2006 at page 10. The Examiner did not address Applicant's arguments regarding the Jacobsen reference.

According to the Examiner, the Fourgoux-Nicol et al. article is no longer applicable because the reason it was initially cited by the Examiner is no longer germane to prosecution. Office Action of October 19, 2006 at page 10. However, the Examiner has ignored the aspects of Fourgoux-Nicol that are germane to prosecution. In particular, paragraphs 17-20 of the Jacobsen Declaration point out that the data in the Fourgoux-Nicol article indicate the *Zea mays* orthologous sequence would hybridize to (and thereby downregulate) a heterologous sequence. The Examiner has not presented any evidence to rebut this conclusion.

The Examiner acknowledged that there are references disclosing the use of antisense or sense suppression technology, but then goes on to state that the "enablement rejection is directed toward the full breadth of the claims." Office Action of October 19, 2006 at page 11. The Examiner then reiterates his statement that the Applicant has not disclosed any partial sequence of the *Zea mays* orthologous gene that can be used to downregulate an endogenous gene in any plant. Office Action of October 19, 2006 at page 11. Thus, the Examiner's position appears to be that since there is a failure to disclose "partial" sequences, claim 20 is not enabled despite Applicant's arguments and the Declaration from Dr. Jacobsen.

The Examiner's argument is wrong on the facts and weak on logic. First, the specification does disclose that partial *Zea mays* orthologous sequences are useful. See, for example, specification at page 30, lines 15-19 and pages 30-32, Examples 3-4.

Second, the Examiner's argument rests on the belief that the supposed "failure" to disclose partial *Zea mays* orthologous sequences outweighs the evidence in the Jacobsen Declaration and in Applicant's Response of July 27, 2006. Applicant's evidence can be summarized as follows. Dr. Jacobsen referred to publications that show the use of heterologous sequences, including sequences having less than 100% sequence identity to an endogenous gene, successfully downregulated the endogenous gene. Dr. Jacobsen concluded that sequences with less than 100% sequence identity can be used for downregulation. Jacobsen Declaration at paragraphs 21-27. The Emery reference is a post-filing date reference that has no evidence of what one skilled in the art would have known on or before the effective filing date. Therefore,

the Emery reference is not relevant to whether the claimed invention would have been enabled as of the effective filing date. In fact, the Emery reference actually demonstrates the precision with which one of ordinary skill can upregulate or downregulate a particular gene. The Jacobsen reference cited by the Examiner reported that there was a significant reduction in overall DNA methylation in the plant lines described in the Jacobsen reference. Jacobsen Declaration at paragraphs 12-14. Dr. Jacobsen was the first author of the Jacobsen reference cited by the Examiner. The Examiner did not respond to Applicant's arguments regarding the Jacobsen reference. Applicant submitted eight additional references that report downregulation using heterologous sequences, including sequences having less than 100% sequence identity to an endogenous gene. Evidence Appendix N. These other prior art references show one of ordinary skill would have concluded that antisense sequences with less than 100% sequence identity can be used to downregulate a heterologous endogenous gene.

Thus, the references cited by the Examiner and the Applicant support enablement. These references demonstrate a high level of skill in the art for downregulation technologies, and that those of ordinary skill knew how to make and use sequences for downregulation. The references demonstrate that the use of these technologies was predictable and required, at most, routine experimentation. These references and the Jacobsen Declaration outweigh the arguments the Examiner put forth.

The Examiner has now asserted that the Applicant has not shown that downregulating any methyltransferase produces seeds with modified endosperm. Office Action of October 19, 2006 at pages 11-12. The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Here, the Examiner did not present a reasonable basis to question enablement. Instead, the Examiner once again misstated the facts by alleging that the specification does not disclose a partial *Zea mays* orthologous sequence that produces seeds with a modified endosperm. In actuality, the specification at page 16, lines 8-28, page 18, lines 26-28 and page 32, lines 6-8, for example, disclose the construction of partial *Zea mays* orthologous sequences linked to a female germ line promoter and the use of such constructs to produce seeds with modified endosperm. The Examiner asserted that "Applicant has not disclosed which regions of the Met1 gene can be used for down-regulating the endogenous gene that will not

down-regulate the other multitude of methyltransferases present in a plant.” Office Action of October 19, 2006 at pages 11-12. The Examiner’s assertion acknowledges the point of Dr. Jacobsen’s Declaration, namely, that partial and full-length *Zea mays* orthologous sequences could be expected to downregulate more than one endogenous DNA methyltransferase in non-*Zea mays* plants. Jacobsen Declaration at paragraphs 22-23. The present inventor recognized that if one targeted expression of partial or full-length *Zea mays* orthologous sequences to the female germ line, one would not need to use specific *Zea mays* ortholog sequences to downregulate specific DNA methyltransferases. In other words, it does not matter for enablement whether more than one DNA methyltransferase is downregulated, and the Examiner has given no reason why it does matter to his enablement rejection.

The Examiner has failed to identify a single reported instance where downregulation of a Met1 gene failed to reduce the degree of methylation. Applicants submit that the reason the Examiner has failed in his effort is because downregulation using the Arabidopsis Met1 sequence and constitutive promoters generally has been successful. As indicated in the Response of July 27, 2006, in the Jacobsen Declaration, and above, Applicant’s claimed method involving the use of targeted promoters and *Zea mays* orthologous sequences would also be expected to be generally successful.

In view of the facts and reasoning above and the record as a whole, the Board is requested to reverse the rejection of claim 62 under 35 U.S.C. §112, first paragraph for lack of enablement.

Claim 63

Claim 63 limits the method of claim 62 to one in which the transcription product comprises an antisense nucleic acid. Applicant traverses the rejection of claim 63 for the reasons given above with regard to claims 62 and 21. The Board is requested to withdraw the rejection of claim 63 for lack of enablement under 35 U.S.C. §112, first paragraph.

Claim 69

Claim 69 limits the method of claim 62 to a transcription product that comprises a full or partial sense copy of the *Z. mays* ortholog sequence. Applicant traverses the rejection of claim 69 for the reasons given above with respect to claims 62 and 66. The Board is requested to withdraw the rejection of claim 69 for lack of enablement under 35 U.S.C. §112, first paragraph.

Claim 76

Claim 76 limits claim 62 to a method in which the plant is a dicotyledonous plant. Applicant traverses the rejection of claim 76 for the reasons given above, in particular, with respect to claims 62 and 64. The Board is requested to withdraw the rejection of claim 76 for lack of enablement under 35 U.S.C. §112, first paragraph.

Claim 86

Claim 86 limits the method claim 62 to one in which the promoter targets expression to female gametic cells. Applicant traverses the rejection of claim 76 for the reasons given above, in particular, with respect to claims 62 and 77. The Board is requested to withdraw the rejection of claim 86 for lack of enablement under 35 U.S.C. §112, first paragraph.

Claim 87

Claim 87 limits claim 86 to a method in which the transcription product comprises an antisense nucleic acid. Applicant traverses the rejection of claim 87 for the reasons given above, in particular, with respect to claims 62, 86 and 21. The Board is requested to withdraw the rejection of claim 87 for lack of enablement under 35 U.S.C. §112, first paragraph.

Claim 88

Claim 88 limits the method of claim 86 to one in which the transcription product comprises a partial sense copy of the Z. mays Met1 ortholog sequence. Applicant traverses the rejection of claim 88 for the reasons given above, in particular, with respect to claims 62, 86 and 67. The Board is requested to withdraw the rejection of claim 88 for lack of enablement under 35 U.S.C. §112, first paragraph.

Claim 89

Claim 89 limits the method of claim 86 to one in which the plant is a dicotyledonous plant. Applicant traverses the rejection of claim 89 for the reasons given above, in particular, with respect to claims 62, 76, and 86. The Board is requested to withdraw the rejection of claim 89 for lack of written description under 35 U.S.C. §112, first paragraph.

Claim 90

Claim 90 limits the method of claim 86 to one in which the plant is a monocotyledonous plant. Applicant traverses the rejection of claim 90 for the reasons given above with respect to

claims 86, 82 and 62. The Board is requested to withdraw the rejection of claim 90 for lack of enablement under 35 U.S.C. §112, first paragraph.

Claim 91

Claim 91 limits the method of claim 89 to one in which the plant is a Brassica plant. Applicant traverses the rejection of claim 91 for the reasons given above with respect to claims 89, 86, 62 and 83. The Board is requested to withdraw the rejection of claim 91 for lack of enablement under 35 U.S.C. §112, first paragraph.

Claim 92

Claim 92 limits the method of claim 89 to one in which the plant is a B. napus plant. Applicant traverses the rejection of claim 92 for the reasons given above with respect to claims 89, 86, 62 and 83. The Board is requested to withdraw the rejection of claim 92 for lack of enablement under 35 U.S.C. §112, first paragraph.

Claim 93

Claim 93 limits the method of claim 90 to one in which the plant is a Zea mays plant. Applicant traverses the rejection of claim 93 for the reasons given above with respect to claims 90, 86, 62 and 85. The Board is requested to withdraw the rejection of claim 93 for lack of enablement under 35 U.S.C. §112, first paragraph.

Conclusion

Applicants respectfully request reversal of the rejection of claims 20-21, 62-67, 69, 71, 76-78 and 80-93, under 35 U.S.C. §112, first and second paragraphs, for indefiniteness, lack of written description and lack of enablement. Please charge the brief fee of \$500 to Deposit Account No. 06-1050. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: April 24, 2007

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Appendix of Claims

20. A method for the production of modified endosperm, which comprises the step of introducing a nucleic acid molecule into a plant, the nucleic acid molecule comprising a promoter that targets expression to female germ line cells and a sequence whose transcription product comprises a partial or full-length *Arabidopsis* DNA methyltransferase 1 (Met1) sequence, wherein the introduced nucleic acid is effective for down-regulating one or more DNA methylating enzymes present in the plant, whereby the degree of DNA methylation of nucleic acid in the plant is reduced as compared to a control plant.

21. A method as claimed in claim 20 wherein the transcription product comprises an antisense nucleic acid.

62. A method for the production of modified endosperm, which comprises the step of introducing a nucleic acid molecule into a plant, the nucleic acid molecule comprising a promoter that targets expression to female germ line cells and a sequence whose transcription product comprises a partial or full-length *Z. mays* DNA sequence orthologous to the *Arabidopsis* DNA methyltransferase 1 (Met1) sequence, wherein the introduced nucleic acid is effective for down-regulating one or more DNA methylating enzymes present in the plant, whereby the degree of DNA methylation of nucleic acid in the plant is reduced as compared to a control plant.

63. A method as claimed in claim 62, wherein the transcription product comprises an antisense nucleic acid.

64. A method as claimed in claim 20, wherein the plant is a dicotyledonous plant.

65. A method as claimed in claim 20, wherein the transcription product down-regulates one DNA methylating enzyme.

66. A method as claimed in claim 20, wherein the transcription product comprises a full or partial sense copy of the *Arabidopsis* DNA methyltransferase 1 (Met1) sequence.

67. A method as claimed in claim 66, wherein the sense copy is a partial sense copy.

69. A method as claimed in claim 62, wherein the transcription product comprises a full or partial sense copy of the *Z. mays* sequence.

71. A method as claimed in claim 66, wherein the plant is a dicotyledonous plant.

76. A method as claimed in claim 62, wherein the plant is a dicotyledonous plant.

77. A method as claimed in claim 20, wherein the promoter targets expression in female gametic cells.

78. A method as claimed in claim 77, wherein the transcription product comprises an antisense nucleic acid.

80. A method as claimed in claim 77, wherein the transcription product comprises a partial sense copy of the *Arabidopsis* DNA methyltransferase 1 (Met1) sequence.

81. A method as claimed in claim 77, wherein the plant is a dicotyledonous plant.

82. A method as claimed in claim 77, wherein the plant is a monocotyledonous plant.

83. A method as claimed in claim 81, wherein the plant is a *Brassica* plant.

84. A method as claimed in claim 81, wherein the plant is a *B. napus* plant.

85. A method as claimed in claim 82, wherein the plant is a *Zea mays* plant.

86. A method as claimed in claim 62, wherein the promoter targets expression to female gametic cells.

87. A method as claimed in claim 86, wherein the transcription product comprises an antisense nucleic acid.

88. A method as claimed in claim 86, wherein the transcription product comprises a partial sense copy of the *Z. mays* sequence orthologous to *Arabidopsis* DNA methyltransferase 1 (Met1) sequence.

89. A method as claimed in claim 86, wherein the plant is a dicotyledonous plant.

90. A method as claimed in claim 86, wherein the plant is a monocotyledonous plant.

91. A method as claimed in claim 89, wherein the plant is a *Brassica* plant.

92. A method as claimed in claim 89, wherein the plant is a *B. napus* plant.

93. A method as claimed in claim 90, wherein the plant is a *Zea mays* plant.

Evidence Appendix

Appendix	Document	Date Entered
A	Genbank Accession Number L10692 [1993]	IDS filed with Response July 27, 2006
B	Finnegan, et al. <u>Nucleic Acids Res.</u> , Vol. 21: pp. 2383-2388 (1993)	IDS filed with Response February 25, 2005 and Office Action mailed January 27, 2006
C	Declaration under 37 CFR § 1.132 of Dr. Steven Jacobsen	Response filed July 27, 2006
D	Finnegan, et al. <u>Ann. Rev. Plant Physiol. Plant Mol. Biol.</u> , Vol. 49: pp. 223-247 (1998)	IDS filed with Response July 27, 2006
E	Alignment of DNA methyltransferase <i>Arabidopsis</i> and <i>Zea mays</i> Nucleotide Sequences (in color)	IDS filed with Response July 27, 2006
F	Genbank Accession Number AF063403 [1998]	IDS with Request for Continued Examination filed November 7, 2005
G	Genbank Accession Number AF007807 [1998]	IDS filed with Response July 27, 2006
H	Genbank Accession Number AF034419 [1998]	IDS filed with Response July 27, 2006
I	Genbank Accession Number AJ002140 [1998]	IDS filed with Response July 27, 2006
J	Fourgoux-Nicol, et al. <u>Plant Molecular Bio.</u> Vol. 40: pp. 857-872 (1999).	Office Action mailed January 27, 2006
K	Emery, et al. <u>Current Biology</u> , Vol. 13: pp. 1768-1774 (2003)	Office Action mailed January 27, 2006
L	Gutterson, <u>HortScience</u> Vol. 30(5): pp. 4-6 (1995)	Office Action mailed January 27, 2006
M	Jacobsen, et al. <u>Current Biology</u> Vol. 10(4): pp. 179-186 (2000)	Office Action mailed October 25, 2004 and January 27, 2006
N	Temple, et al. <u>Mol. Gen. Genet</u> Vol. 236(3): pp. 315-325 (1993); Oliver, M.J., et al. <u>Mol. Gen. Genet.</u> Vol. 239(2): pp. 425-434 (1993); Van der Krol, A.R., et al., <u>Nature</u> Vol. 333: pp. 866-869 (1988); Carron, et al. <u>Theoretical and Applied Genetics</u> Vol. 87(8): pp. 1006-1015 (1994); Einset, J.W., <u>Plant Cell Tissue and Organ Culture</u> Vol. 46(2): pp. 137-141 (1996); Trevanion, et al. <u>Plant Physiol.</u> Vol. 113(4): pp. 1153-1165 (1997); Faskce, et al. <u>Plant Physiol.</u> Vol. 115(2): pp. 705-715 (1997); Herbiik, et al. <u>Eur. J. Biochem.</u> 265(1): pp. 231-239 (1999); Veena, et al. <u>Plant Journal</u> 17(4): pp. 385-395 (1999).	IDS filed with Response July 27, 2006

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Related Proceedings Appendix

None